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(21) International Application Number: PCT/EP96/03601 (22) International Filing Date: 16 August 1996 (16.08.96) (30) Priority Data: 9517022.1 19 August 1995 (19.08.95) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): McDADE, Hugh, Brownlie [GB/GB]; Glaxo Wellcome plc, Greenford Road, Greenford, Middlesex UB6 0HE (GB). (74) Agent: QUILLIN, Helen, K.; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: 1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES IN THE TREATMENT OF HEPATITIS C			
(57) Abstract The present invention relates to the use of nucleoside analogues in the treatment of viral infections. More specifically it is concerned with the use of 1,3-oxathiolane nucleoside analogues in the treatment of hepatitis C.			

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1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES IN THE TREATMENT OF HEPATITIS C

The present invention relates to the use of nucleoside analogues in the treatment of viral infections. More specifically it is concerned with the use of 1, 3-oxathiolane nucleoside analogues in the treatment of hepatitis C.

Hepatitis C, formerly known as non-A-non-B hepatitis (NANB hepatitis), is a viral disease believed to be transmitted parenterally by contaminated material such as blood and blood products, contaminated needles, sexually and vertically from infected or carrier mothers to their off-spring.

The disease is commonly associated with transfusion of blood or blood products and is now a much more common cause of post-transfusion hepatitis than is hepatitis B. In countries where it is common to administer medicaments by intramuscular injection there is a high incidence of hepatitis C.

PCT patent application publication number WO 91/17159 specifically describes the compound (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one (also known as lamivudine) and its use in the treatment of HIV infections.

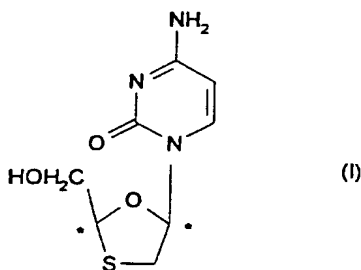
Lamivudine is the (-)-enantiomer of the racemate BCH-189 specifically described in EPA 0382526.

PCT patent application publication number WO92/11852, describes the use of BCH-189 and its individual enantiomers, including lamivudine, for the treatment of hepatitis B.

We have now found that BCH-189 and its individual enantiomers including lamivudine are active against the hepatitis C virus.

The invention accordingly provides, in a first aspect, a method for the treatment of an animal, including man, infected with or susceptible to infection with the hepatitis

C virus comprising the administration of an effective amount of a compound of formula (I)



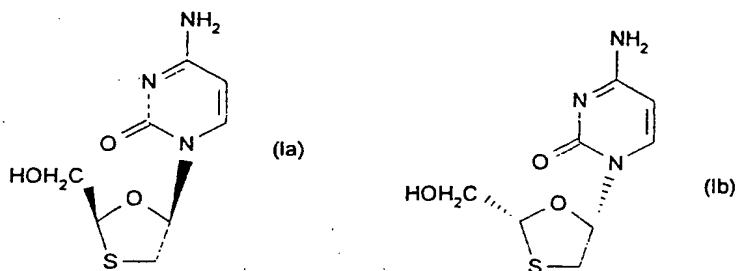
5 or a pharmaceutically acceptable derivative thereof.

In a further or alternative aspect there is provided a compound of formula (I) as defined hereinabove or pharmaceutically acceptable derivative thereof for use in the manufacture of a medicament for the treatment of hepatitis C.

10

As will be appreciated by those skilled in the art references herein to treatment extend to prophylaxis as well as to the treatment of established infections or symptoms.

15 As will be appreciated by those skilled in the art the compound of formula (I) is a cis compound and contains two chiral centres (shown in formula (I) by *). Thus the compound exists as two enantiomers, compound of formulae (Ia) and (Ib) respectively.



The compound of formula (I) is preferably in the form of a racemic mixture or its (-)-enantiomer (compound of formula (Ib)) but a mixture of compounds of formulae (Ia) and (Ib) in any ratio may be employed in the invention.

5

The compound of formula (I) has the chemical name cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. It is also known as BCH-189. The (-)-enantiomer has the chemical name (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and has the absolute stereochemistry of the compound of formula (Ib) which has the name (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. It is also known as lamivudine.

15 Preferably when the (-)-enantiomer is employed it will be substantially free of the corresponding (+)-enantiomer, that is to say no more than about 5% w/w of the (+)-enantiomer, preferably no more than about 2%, in particular less than about 1% w/w will be present.

20 By the term "pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an antivirally active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified, to provide pharmaceutically acceptable derivatives thereof, at functional groups in both the base moiety and at the hydroxymethyl group of the oxathiolane ring. Modification at all such functional groups are included within the scope of the invention. However, of particular interest are pharmaceutically acceptable derivatives (e.g. esters) obtained by modification of the 2-hydroxymethyl group of the oxathiolane ring.

Preferred esters of the compounds of formula (I) include the compounds in which OH is replaced by a carboxyl function $RC(=O)$ in which the non-carbonyl moiety R of the ester grouping is selected from hydrogen, straight or branched chain alkyl (e.g. methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g. methoxymethyl) aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxymethyl), aryl (e.g. phenyl optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy); substituted dihydro pyridinyl (e.g. N-methyldihydro pyridinyl); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g. methanesulphonyl); sulphate esters, amino acid esters (e.g. L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters.

Also included within the scope of such esters are esters derived from polyfunctional acids such as carboxylic acids containing more than one carboxyl group, for example, dicarboxylic acids $HO_2C(CH_2)_nCO_2H$ where n is an integer of 1 to 10 (for example, succinic acid) or phosphoric acids. Methods for preparing such esters are well known. See, for example, Hahn et al., "Nucleotide Dimers as Anti Human Immunodeficiency Virus Agents", Nucleotide Analogues, pp. 156-159 (1989) and Busso et al., "Nucleotide Dimers Suppress HIV Expression In Vitro", AIDS Research and Human Retroviruses, 4(6), pp. 449-455 (1988).

With regard to the above described esters, unless otherwise specified any alkyl moiety present advantageously contains 1 to 16 carbon atoms, particularly 1 to 4

carbon atoms and could contain one or more double bonds. Any aryl moiety present in such esters advantageously comprises a phenyl group.

5 In particular the esters may be a C₁₋₁₆alkyl ester, an unsubstituted benzoyl ester or a benzoyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), C₁₋₆alkyl, saturated or unsaturated C₁₋₆alkoxy, nitro or trifluoromethyl groups.

10 Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic,
15 while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

20 Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR₄⁺ (where R is C₁₋₄alkyl) salts.

References hereinafter to a compound according to the invention includes both the compound of formula (I) and its pharmaceutically acceptable derivatives.

25 The compound of formula (I) and its individual enantiomers may be prepared by any method known in the art for the preparation of compounds of analogous structure for example by the methods described in EPA 0 382 526, WO 91/ 17159 or WO92/20669, each of which is incorporated herein by reference.

It will be appreciated that the amount of a compound of formula (I) required for use in treatment will vary with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.1 to about 750mg/kg of bodyweight per day preferably in the range of 0.5 to 60 mg/kg/day, most preferably in the range of 1 to 20mg/kg/day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 1500mg, conveniently 20 to 1000mg, most conveniently 50 to 700mg of active ingredient per unit dosage form. Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of form about 1 to about 75.M, preferably about 2 to 50.M, most preferably about 3 to 30.M. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to 100mg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

A pharmaceutical formulation will comprise a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a pre-determined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary, or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives

such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

- The compounds for use according to the invention may also be formulated for
- 5 parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such
- 10 as suspending, stabilising and /or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by a aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle e.g. sterile, pyrogen-free water, before use.
- 15 For topical administration to the epidermis a compound of formula (I) may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more
- 20 emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or

25 tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other commonly used materials in the art, and the suppositories may be conveniently formed by admixture of the active compound
5 with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, paste, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be carriers.
10

For intra-nasal administration the compounds of formula (I) may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents. Liquid
15 sprays are conveniently delivered from pressurised packs.

For administration by inhalation the compounds for use according to the invention are conveniently delivered from an insufflator, nebuliser or a pressure pack or
20 other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

25

Alternatively, for administration by inhalation or insufflation, the compounds for use according to the invention may take the form of a dry powder composition, for example a powder mix compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for

example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release
5 of the active ingredient may be employed.

The pharmaceutical compositions for use in the present invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

10 Suitable formulations for use in the invention are described for example in EPA 0382526 and WO 91/17159.

A compound of formula (I) may also be used in accordance with the invention in combination with other therapeutic agents for example other antiinfective agents.
15 In particular the compounds of the invention may be employed together with known antiviral agents. For example, the compound of formula (I) may be used in combination with an interferon, which may be recombinant or lymphoblastoid, such as interferon- α , β or δ , preferably interferon- α , or with ribavirin, or with thymosin alpha.

20

The combination referred to above may be conveniently be presented for use in the form of pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefore comprise a further aspect of the invention.

25

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Experimental Data

Protocol: 10 human subjects were given 300mg of lamivudine twice daily for 12 weeks with a 12-week follow-up period. 9 of the original 10 participants completed the full 12-week course of treatment.

The following two values were measured from blood serum samples provided at baseline, week 2, week 4, week 8 and week 12 during the 12-week dosing period and at week 14 and every 4 weeks thereafter during the follow-up period.

Alanine amino transferase (ALT) was measured by enzyme kinetic methodology using a UV spectrophotometric test with pyridoxal phosphate co-factor.

HCV RNA was measured by quantitative PCR using 5' non-coding primers and chemiluminescence detection as described by Brilliant S. et al. Gastroenterology 1994; 107: 812-817.

Results:

ALT Response: An overall decreasing trend in median ALT was detected with one patient showing a steady decrease through the treatment. The results are plotted at Figure 1 as Median ALT (IU/L) against Time (weeks).

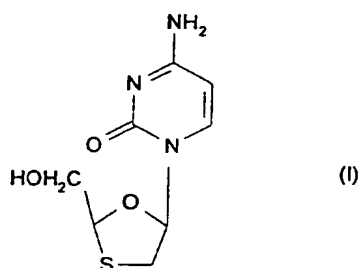
HCV RNA Response: Median HCV RNA levels fell from the initial baseline value during the treatment period with two patients experiencing a ≥ 2 log 10 reduction from baseline at the end of the treatment (week 12). The results are plotted at Figure 2 as Median HCV RNA (Log 10 Genomes/ml) at Each Visit against Time

5 (Weeks).

13

CLAIMS:

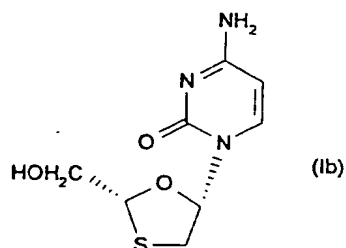
1. A compound of formula (I)



5

or a pharmaceutically acceptable derivative thereof for use in the manufacture of a medicament for the treatment of hepatitis C.

- 10 2. A compound of formula (Ib)



- 15 substantially free of the corresponding enantiomer or a pharmaceutically acceptable derivative thereof for use in the manufacture of a medicament for the treatment of hepatitis C.

3. A compound of formula (I) as claimed in claim 1 or a compound of formula (Ib) as claimed in claim 2 or pharmaceutically acceptable derivatives

thereof in the manufacture of a medicament for administration simultaneously or sequentially with another antiviral agent active against hepatitis C virus.

4. A method of treatment of an animal infected with or susceptible to
5 infection with the hepatitis C virus comprising the administration of an effective amount of a compound of formula (I), as defined in claim 1, or formula (Ib), as defined in claim 2.
5. A method of treatment as claimed in claim 4 wherein the compound of
10 formula (I) or of formula (Ib) is administered simultaneously or sequentially with another antiviral agent active against hepatitis C virus.
6. A pharmaceutical formulation comprising a compound of formula (I) as
15 defined in claim 1 or of formula (Ib) as defined in claim 2 for use in the treatment of hepatitis C.
7. A pharmaceutical formulation comprising a combination of a compound of formula (I) as defined in claim 1 or of formula (Ib) as defined in claim 2 and another antiviral agent active against hepatitis C virus.

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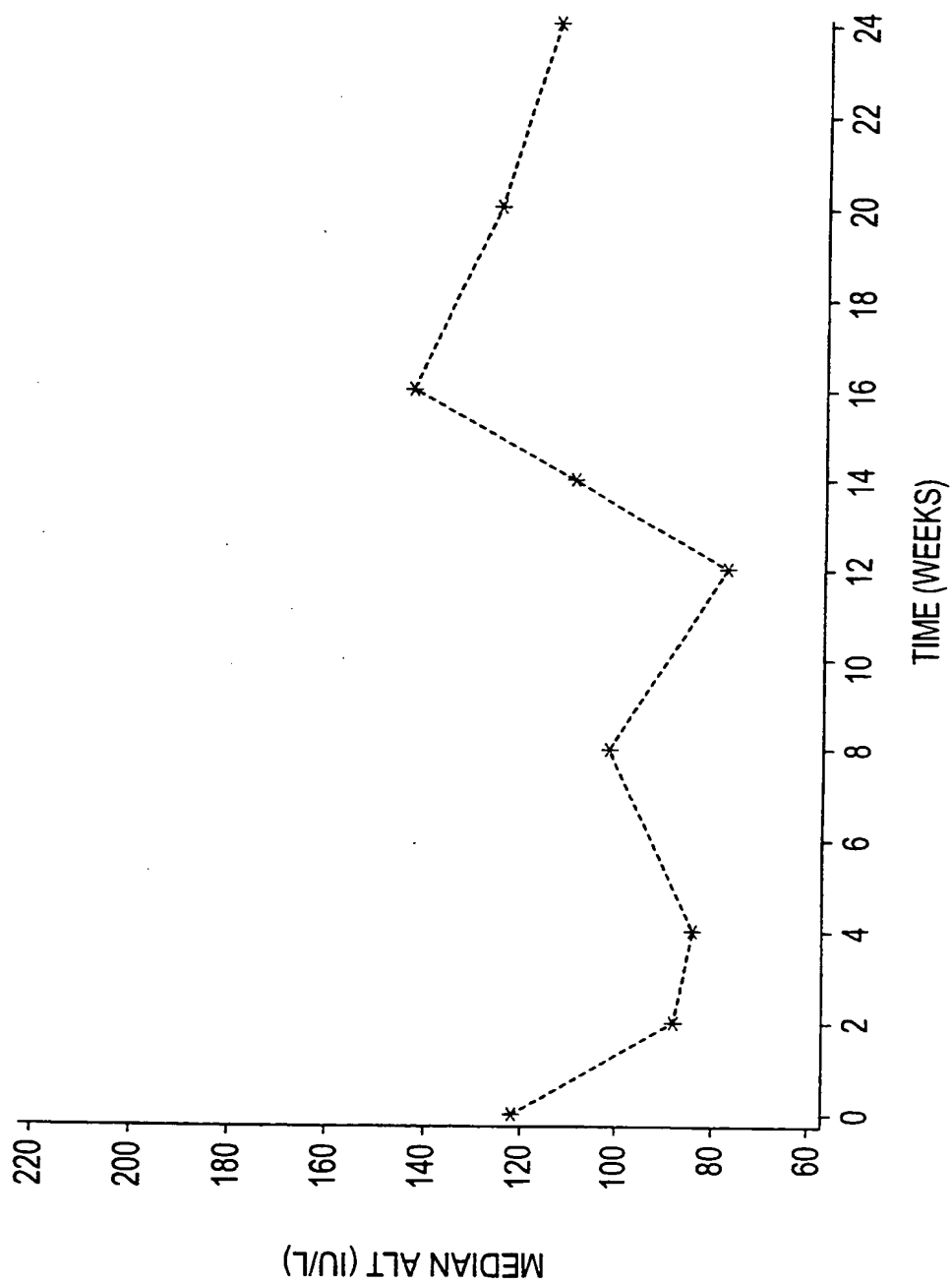


Fig.1 MEDIAN ALT (IU/L) AT EACH VISIT: INTENT-TO-TREAT POPULATION

2/2

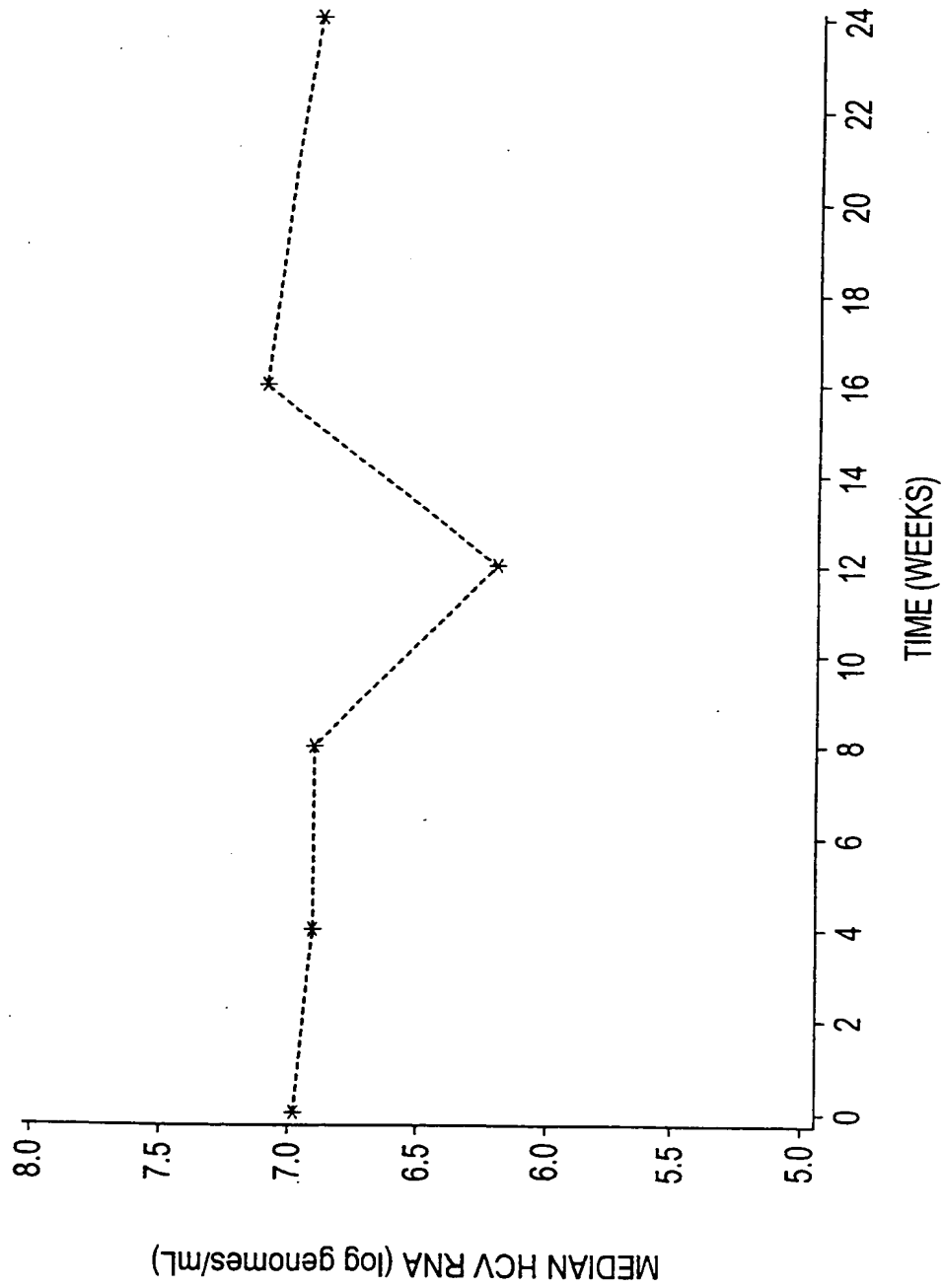


Fig.2 MEDIAN HCV RNA (LOG 10 GENOMES/ML) AT EACH VISIT: INTENT-TO-TREAT POPULATION

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03601

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K31/505		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 11852 (IAF BIOCHEM INT. ET AL.) 23 July 1992 cited in the application see page 13 - page 14; claims 1-9 see page 8, line 20 - line 22	1-3,6
Y		7
X	SOUTH AFRICAN MED J, vol. 84, no. 8II, 1994, pages 563-570, XP002019764 DUSHEIKO: "management of chronic hepatitis b and c" see page 566; table I see page 567, right-hand column, paragraph 2	1-3,6
Y		7
A	see page 567, right-hand column, paragraph 3 - page 569	4,5
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 29 November 1996		Date of mailing of the international search report 11.12.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016		Authorized officer Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/03601

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US biosis number: 99126202, 1996 SINCLAIR ET AL.: "benefits and safety of lamivudine (3TC) therapy in HIV positive patients with chronic hepatitis B or C" XP002019880 see abstract</p>	1-7
X,P	<p>& ELEVENTH INTERNATIONAL CONFERENCE ON AIDS,VANCOUVER,BRITISH COLUMBIA, CANADA, JULY 7-12 1996, 1996, page 287 SINCLAIR ET AL.: -----</p>	1-7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/03601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 4,5
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/03601

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9211852	23-07-92	AT-T- 120644	15-04-95
		AU-B- 660650	06-07-95
		AU-A- 1153492	17-08-92
		CA-A- 2100269	04-07-92
		DE-D- 69201948	11-05-95
		DE-T- 69201948	03-08-95
		EP-A- 0494119	08-07-92
		EP-A- 0565549	20-10-93
		ES-T- 2070628	01-06-95
		HK-A- 159395	20-10-95
		IL-A- 100502	08-12-95
		JP-T- 6507150	11-08-94
		US-A- 5532246	02-07-96